EXHIBIT 3

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[54] NUCLEOTIDE SEQUENCES DERIVED FROM THE GENOME OR RETROVIRUSES OF THE HIV-1, HIV-2, AND SIV TYPE, AND THEIR USES IN PARTICULAR FOR THE AMPLIFICATION OF THE GENOMES OF THESE RETROVIRUSES AND FOR THE IN VITRO DIAGNOSIS OF THE DISEASES DUE TO THESE VIRUSES

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Related U.S. Application Data

[62] Division of Ser. No. 160,465, Dec. 2, 1993, Pat. No. 5,688,637, which is a continuation of Ser. No. 820,599, Jan. 21, 1992, abandoned.

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[52] U.S. Cl. 435/69.3; 536/23.72
[58] Field of Search 536/23.72; 435/320.1, 435/69.3

[56] References Cited

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OTHER PUBLICATIONS

Guyader et al., *Nature*, vol. 326, 1987, pp. 662–669.
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[57] ABSTRACT

The invention relates to nucleotidic sequences derived from genomes of the HIV-1 type virus, or from genomes of the HIV-2 type virus, or of the SIV type virus, and their applications, especially as oligonucleotidic initiators of implementation of an (in vitro) method for the diagnosis of the infection of an individual by a virus of the HIV-1 and/or HIV-2 type.

2 Claims, No Drawings

or (particularly in the case of the longest sequences) contains one of the above-mentioned nucleotide sequences derived from HIV-1 Bru or HIV-1 Mal. or HIV-1 Eli or HIV-2 ROD or SIVMac. or contains a complementary nucleotide sequence of one of these latter sequences. it being understood that the possible additional nucleotides which "extend beyond" the nucleotide sequence of the type in question at the 3' or 5' ends preferably coincide with those which are placed external to the 5' or 3' end of the same sequence within the complete sequence of the viruses of the HIV-1. HIV-2 or SIV MAC type mentioned above.

or. if this nucleotide sequence is not identical with one of the above-mentioned nucleotide sequences. or is not complementary to one of these sequences. it is nonetheless capable of hybridizing with a nucleotide sequence derived from the viruses HIV-1 Bru. HIV-1 Mal. HIV-1 Eli and/or with a nucleotide sequence derived from the viruses HIV-2 ROD or SIV MAC mentioned above. The hybridization may be carried out at a temperature of 60° C.±1° C. (preferably 60° C.±0.5° C.). recommended for an optimal yield.

The numbering of the nucleotides mentioned below corresponds to that used in the reference manual "Human Retrovirus and AIDS-1989" edited by the "Los Alamos National Laboratory-New Mexico-USA".

(The sequences of the viruses HIV-1 Mal. HIV-1 Eli were described by MONTAGNIER. SONIGO. WAIN-HOBSON and ALIZON in the European patent application No. 86.401380 of 23 Jun.. 1986).

The sequences of the invention are synthesized in a synthesizer marketed by Applied Biosystems (phosphoroamidite method) or in any other apparatus employing a similar method.

The invention relates more particularly to the oligonucleotide sequences characterized by the following nucleotide sequences (shown in the 5'→3' sense; the initials "S" and "AS" indicate whether the oligonucleotide is sense or antisense. i.e. whether the oligonucleotide is oriented in the 5'→3' or in the 3'→5' sense): 1°) sequences common to the genomes of the HIV-1. HIV-2 and SIV viruses (the pairs of numbers separated by a dash indicate the position of the nucleotides in the genomes corresponding respectively to the viruses HIV-1 Bru. HIV-1 Mal. HIV-1 Eli. HIV-2 ROD and SIV):

specific sequences of the gag gene of the genome of the above-mentioned viruses (gene coding for a group of antigens specific for the nucleoid of these viruses).

Certain variants may be introduced by certain positions of the nucleotide sequences indicated below. without affecting the hybridization properties of these nucleotide sequences with the genes of the viruses of the HIV and/or SIV types. The nucleotide sequences containing these variants are shown below the original nucleotide sequences from which they are derived by substitution of one or more bases. The bases representing modifications of the initial nucleotide sequences are indicated by a letter directly beneath the base which they replace in the initial sequences; whereas the bases of the original sequences which are not replaced in the sequences bearing these variants are shown by dots.

The synthesis of the primers is carried out by using all of the variants simultaneously. It is the mixture of all of the variants for a given sequence which is used in the tests.

MMy1: TGG CGC CCG AAC AGG GAC
... ... .T. ... ...
S, 636-653, 635-652, 636-653, 859-876, 834-851

MMy2: GGC CAG GGG GAA AGA AAA A
... .C. .C. ... ...
... ... .A. ... ...
S, 854-872, 864-888, 848-872, 1160-1184, 1124-1148

MMy3: TGC CCA TAC AAA ATG TTT TA
... ... C.. T.T ... .
AS, 900-881, 916-897, 900-881, 1212-1193, 1176-1157

MMy4: TGC ATG GCT GCT TGA TG
... ..A ... ..C ..G ..
AS, 1385-1369, 1419-1403, 1385-1369, 1703-1687, 1667-1651

MMy4B: CTT TGC ATG GCT GCT TGA TG
..C ... ..A ... ..C ..G ..
AS, 1388-1369, 1421-1403, 1388-1369, 1706-1687, 1670-1651,

MMyBa: CAT CAA GCA GCC ATG CAA AG
..C ..G ... ..T ... ..G ..
S, 1369-1388, 1403-1421, 1369-1388, 1687-1706, 1651-1670,

MMy28: AGG GCT GTT GGA AAT GTG G
... ...G ... .
S, 2021-2039, 2055-2073, 2024-2042, 2329-2349, 2299-2318,

MMy28a: CCA CAT TTC CAG CAT CCC T
... ...G ... .
... ...C ... .
AS, 2039-2021, 2073-2055, 2042-2024, 2349-2329, 2318-2299

. specific sequences of the vpr gene:

MMy18: GAT AGA TGG AAC AAG CCC CAG
S, 5590-5610, 5585-5605, 5554-5574, 6233-6296, 6147-6170,

MMy19: TCC ATT TCT TGC TCT CCT CTG T
AS, 5870-5849, 5865-5844, 5834-5813, 6551-6531, 6454-6431,

. specific sequences of the pol gene:

MMy29: TAA AGC CAG GAA TGG ATG GCC CAA

-continued

MMy9:	ATG GGT GGC AAG TGG TCA AAA AGT AG	
	... ...A	
	S, 8844-8869, 8836-8861, 8787-8812,	
MMy9a:	CTA CTT TTT GAC CAC TTG CCA CCC AT	
	AS, 8869-8844, 8861-8836, 8812-8787,	
MMy78:	TAT TAA CAA GAG ATG GTG G	
	S, 7629-7647, 7612-7630, 7572-7590,	
MMy89:	CCA GCA AGA AAA GAA TGA A	
	S, 8224-8242, 8213-8231, 8167-8185,	
MMy89a:	TTC ATT CTT TTC TTG CTG G	
	AS, 8242-8224, 8231-8213, 8185-8167,	
. specific sequences of the nef 1 gene:		
MMy10:	AAA AGA AAA GGG GGG ACT GGA	
	S, 9116-9136, 9117-9137, 9062-9082,	
MMy10a:	TCC AGT CCC CCC TTT TCT TTT	
	AS, 9136-9116, 9137-9117, 9082-9062,	
MMy11:	AAA GTC CCC AGC GGA AAG TCC C	
	AS, 9503-9483, 9505-9484, 9449-9428,	
. specific sequences of the vif 1 gene:		
MMy15:	GAT TAT GGA AAA CAG ATG GCA GGT GAT	
	S, 5073-5099, 5068-5094, 5037-5063,	
MMy16:	GCA GAC CAA CTA ATT CAT CTG TA	
	S, 5383-5405, 5378-5400, 5347-5369,	
MMy16a:	TAC AGA TGA ATT AGT TGG TCT GC	
	AS, 5405-5383, 5400-5378, 5369-5347,	
MMy17:	CTT AAG CTC CTC TAA AAG CTC TA	
	AS, 5675-5643, 5670-5648, 5639-5617,	
.specific sequences of the vpu gene		
MMy25:	GTA AGT AGT ACA TGT AAT GCA ACC T	
	S, 6081-6105, 6076-6100, 6045-6069,	
MMy26:	AGC AGA AGA CAG TGG CCA TGA GAG	
	S, 6240-6263, 6238-6261, 6207-6230,	
MMy27:	ACT ACA GAT CAT CAA TAT CCC AA	
	AS, 6343-6321, 6338-6316, 6307-6285,	

The object of the invention is also the sequences (or primers) possessing a complementary nucleotide structure to those of the primers defined above.

It also relates to the nucleotide sequences possessing certain mutations with respect to those defined above without the hybridization properties, such as defined above, of these sequences being modified. The percentage of nucleotides different from those constituting the sequences described above without thereby affecting the hybridization properties of the sequences of the invention may attain 40%.

Generally speaking, in the case of a sense (S) primer, a larger number of mutations is tolerated at the 5' end than at the 3' end of the primer, the 3' end being required to hybridize perfectly with a specific strand of a nucleotide sequence in order for this sequence to be amplified. In the case of an anti-sense (AS) primer, it is at the 3' end that tolerance is allowed.

The object of the invention is also the primers such as those defined above and including a conserved stretch of at least 5 bases on either side of the central part which contains modifications without the above hybridization properties being modified.

One of the characteristics of the oligonucleotide primers of the invention is that of giving a clear-cut amplification band, usually free of aspecific bands when the technical directions for use described in the present invention are followed. This fact is due to the length of the primers which may attain 27 bases and thus increases the specificity of hybridization, as well as to the drastic conditions of use which make it possible to eliminate parasitic combinations. In addition to the percentage of homology with the reference matrix, the specificity for each type of virus is a function of the length of the primer which may attain as many as 40 bases in order to obtain an acceptable yield.

The invention also includes primers such as those described above linked at their 5' end to a promoter for the implementation of a method of genomic amplification by the synthesis of multiple copies of DNA or RNA such as that described in the European patent application No. 88/307.102.9 of 01 Aug., 1988.

The object of the invention is in particular the use of the primers described above for the implementation of a procedure of gene amplification of nucleotide sequences of the viruses of the HIV-1 and/or HIV-2 and/or SIV type, this procedure being applicable to the in vitro diagnosis of the potential infection of an individual by a virus of the HIV-1 and/or HIV-2 type or of an animal by at least one of the three viruses (HIV-1, HIV-2, SIV).

This method of in vitro diagnosis of the invention is carried out starting from a biological sample (for example a biological fluid such as serum, the lymphocytes of circulating blood) obtained from a patient under study, and comprising mainly the following steps:

- a step involving the extraction of the nucleic acid to be detected belonging to the genome of the virus of the HIV-1 and/or HIV-2 and/or SIV type possibly present in the above-mentioned biological sample and, where appropriate, a step involving the incubation of the said nucleic acid with a reverse transcriptase if this latter is in the form of RNA in order to obtain a double-stranded nucleic acid (this last step being also designated below as the step of retrotranscription of the viral RNA),
- a cycle comprising the following steps:
  - denaturation of the double-stranded nucleic acid to be detected, which leads to the formation of a single stranded nucleic acid,
  - hybridization of each of the strands of the nucleic acid obtained during the previous denaturation step with at least one primer according to the invention, by placing the strands mentioned above with at least one primer couple according to the invention under the conditions of hybridization defined below.

The optimal concentration of DNA is 100 to 300 ng in the case of genomic DNA extracted from cells (of patients or in culture, mammals or other species).

It is obvious that the preceding conditions represent optimal conditions for a final reaction mixture of 50 µl, and that these conditions may be modified, depending on the final volume of the reaction mixture.

The use of several different primer couples (or cocktails of couples) of the invention makes possible either the cross-detection of several types of the viruses of the HIV and/or SIV type, or the simultaneous detection of several genes of a given virus of the HIV and/or SIV type.

As examples of the preferred primer couples which can be used within the framework of the present invention, mention may be made of the following primer couples:

MMy1–MMy4, MMy2–MMy4, MMy1–MMy3, MMy18–MMy19, MMy4a–MMy28a, MMy28–MMy29a, MMy29–MMy30a, MMy31–MMy32a, in particular for the in vitro diagnosis of the infection of an individual by HIV-1 and/or HIV-2

MMy5–MMy8, MMy6–MMy8, MMy7–MMy8, MMy5–MMy7a, MMy6–MMy7a, MMy9–MMy11, MMy10–MMy11, MMy9–MMy10a, MMy26–MMy5a, MMy8a–MMy9a, MMy8a–MMy89, MMy89a–MMy 9a, MMy15–MMy17, MMy15–MMy16a, MMy16–MMy17, MMy25–MMy27, MMy26–MMy27, in particular for the in vitro diagnosis of the infection of an individual by HIV-1,

MMy20–MMy22, MMy20–MMy21a, MMy21–MMy22, MMy23–MMY24, MMy12–MMy14, MMy12–MMy13a, for the in vitro diagnosis of the infection of an individual by HIV-2.

The agent of polymerization used in the elongation step of the cycle is a thermostable DNA polymerase, in particular Taq polymerase, the amplifiose of the Appligene company or any thermostable DNA polymerase which is commercially available.

Generally speaking, the cycle of the method of in vitro diagnosis of the invention is repeated between 30 and 40 times.

Depending on the nucleotide primer couples used, the method of in vitro diagnosis of the invention also makes it possible to detect selectively the genes of the viruses of the HIV and/or SIV type present in the biological sample.

As examples of the primer couples which can be used for the above-mentioned method of diagnosis gene-per-gene of the invention are the following:

MMy1–MMy4, MMy2–MMy4, MMy1–MMy3, MMy4a–MMy28a for the gag gene,

MMy18–MMy19 for the vpr gene,

MMy5–MMy8, MMy6–MMy8, MMy7–MMy8, MMy5–MMy7a, MMy6–MMy7a, MMy26–MMy5a, MMy8a–MMy9a, MMy8a–MMy89, MMy89a–MMy9a for the env gene,

MMy9–MMy11, MMy9–MMy10a, MMy10–MMy11 for the nef1 gene,

MMy15–MMy17, MMy15–MMy16a, MMy16–MMy17 for the vif1 gene,

MMy20–MMy22, MMy20–MMy21a, MMy21–MMy22 for the vif 2 gene,

MMy23–MMy24 for the vpx gene,

MMy12–MMy14, MMy12–MMy13a, MMy13–MMy14 for the nef2 gene,

MMy25–MMy27, MMy26–MMy27 for the vpu gene,

MMy28–MMy29a, MMy29–MMy30a, MMy30–MMy31a, MMy31–MMy32a for the pol gene.

However, the combinations between "S" and "AS" primers described above are not limiting and may be varied according to the wish of the user.

The sizes of the nucleotide fragments synthesized with the aid of the primer couples mentioned above as examples are shown in the following Tables I to XI:

(the figures indicated in the Tables below represent the number of nucleotides in the fragments synthesized, and the "dashes" indicate that the primer couples tested do not make it possible to characterize the corresponding viral strains).

TABLE I

	gag		gag	
	MMy1-MMy3	MMy1-MMy4	MMy2-MMy4	MMy4a-MMy28a
HIV1-BRU	265	750	532	671
HIV1-MAL	282	785	556	671
HIV1-ELI	265	750	538	674
HIV2-ROD	354	845	544	663
SIV	343	844	544	668

TABLE II

	env		env	
	MMy5-MMy7a	MMy5-MMy8	MMy6-MMy7a	MMy6-MMy8
HIV1-BRU	480	953	330	803
HIV1-MAL	471	944	321	794
HIV1-ELI	471	941	321	791
HIV2-ROD	—	—	—	—
SIV	—	—	—	—

TABLE III

	env		env
	MMy7-MMy8	MMy26-MMy5a	MMy8a-MMy9a
HIV1-BRU	498	691	1038
HIV1-MAL	498	691	1041
HIV1-ELI	495	679	1038
HIV2-ROD	—	—	—
SIV	—	—	—

TABLE IV

	env	env
	MMy8a-MMy89	MMy89a-MMy9a
HIV1-BRU	411	646
HIV1-MAL	411	649
HIV1-ELI	411	646
HIV2-ROD	—	—
SIV	—	—

infection of monkeys (macaque, mangabey monkey or green monkey) by the virus of the SIV type, this method duplicating the principal characteristics of that described above.

The object of the invention is also diagnostic kits for the implementation of the methods of in vitro diagnosis mentioned above. As an example, a diagnostic kit of the present invention contains:

- at least one oligonucleotide primer couple according to the invention, each couple consisting of a primer which hybridizes with one of the strands of the nucleic acid sequence to be detected, and a primer which hybridizes with the complementary strand of this latter under the conditions defined above,
- suitable reagents for the implementation of the cycle of amplification operations, in particular a DNA polymerase and the four different nucleoside triphosphates, and the reaction medium designated "10× buffer" described above,
- one (or more) probe which can be labelled, in particular by radioactivity, and which is capable of hybridizing specifically in the labelled or unlabelled form with the amplified nucleic acid sequence(s) to be detected.

The invention also relates to the use of the primers of the invention indicated above for the implementation of a procedure for the synthesis of proteins encoded in the nucleotide sequences amplified by means of these primers.

As an illustration, this procedure for the synthesis of proteins comprises the amplification of the nucleotide sequences of the genomes of the viruses of the HIV or SIV type (coding for a specific protein and, where appropriate, having undergone certain modifications of their nucleotides) by placing in contact the said sequences with at least one primer couple according to the invention under the conditions described above, followed by the translation of these sequences thus amplified into proteins; this last step is carried out in particular by transformation of suitable host cells with the aid of vectors containing the said amplified sequences, and the recovery of the proteins produced in these host cells.

The invention also relates to the polypeptides derived from the translation of the nucleotide sequences (or primers) of the invention.

The object of the invention is also the use of the anti-sense oligonucleotide primers as antiviral agents in general, in particular to combat AIDS, as well as pharmaceutical compositions containing these anti-sense primers in combination with a pharmaceutically acceptable vehicle.

The invention also relates to the immunogenic compositions containing one or more translation products of the nucleotide sequences according to the invention, and/or one or more translation products of the nucleotide sequences amplified according to the procedures described above starting from primers defined according to the invention, these translation products being combined with a pharmaceutically acceptable vehicle.

The invention relates to the antibodies directed against one or more of the translation products described above (or, in other terms, capable of giving rise to an immunological reaction with one or more translation products of the nucleotide sequences according to the invention, or also one or more translation products of the amplified nucleotide sequences starting from primers defined according to the invention) and their use for the implementation of methods of in vitro diagnosis of the infection of an individual by a virus of the HIV-1 and/or HIV-2 type, or of an animal by at least one of the three viruses (HIV-1, HIV-2, SIV) according to the procedures well-known to the person skilled in the art.

As an illustration, such a method of in vitro diagnosis according to the invention comprises the placing in contact of a biological sample (in particular serum), taken from a patient under study, with antibodies according to the invention, and the detection by means of any appropriate procedure (in particular with the aid of labelled anti-immunoglobulins) of the immunological complexes formed between the antigens of the viruses of the HIV or SIV type possibly present in the biological sample and the said antibodies.

The object of the invention is also kits for in vitro diagnosis containing antibodies according to the invention and, where appropriate, suitable reagents for the detection of the immunological complex formed by reaction between the said antibodies and the antigens of the HIV or SIV viruses.

The invention also relates to a procedure for the preparation of the polypeptides mentioned above, in particular those corresponding according to the universal genetic code to the nucleotide sequences (or primers) described above, this procedure being characterized in that, starting preferably from the C-terminal amino acid, successive amino acid residues are condensed successively one at a time in the required order, or amino acid residues and fragments previously formed and already containing several amino acid residues in the required order are condensed, or also several fragments thus prepared beforehand are condensed, it being understood that care will be taken to protect beforehand all of the reactive functions borne by these amino acid residues or fragments with the exception of the amine function of the one and the carboxyl function of the other, which normally must participate in the formation of the peptide bonds, in particular after activation of the carboxyl function according to the known methods of peptide synthesis and this is continued in a stepwise manner until the N-terminal amino acid is reached.

For example, recourse may be had to the procedure of peptide synthesis in homogeneous solution described by Houbenweyl in "Methoden der Organischen Chemie" (methods of Organic Chemistry) edited by W. Wunsch, vol. 15-I and II, THIEME, STUTTGART, 1974, or to that of peptide synthesis on a solid phase described by R. D. Merrifield in "Solid Phase Peptide Synthesis" (*J. Am. Chem. Soc.*, 45, 2149–2154).

The invention also relates to a procedure for the preparation of the nucleotide sequences (or primers) described above, this procedure comprising the following steps:

- incubation of the genomic DNA, isolated from one of the viruses of the HIV or SIV type mentioned above, with DNAase I, then addition of EDTA and purification by extraction with the mixture phenol/chloroform/isoamyl alcohol (25/24/1), then by ether,
- treatment of the DNA thus extracted by Eco R1 methylase in the presence of DTT, and purification by extraction as described above,
- incubation of the DNA thus purified with the 4 deoxynucleoside triphosphates dATP, dCTP, dGTP and dTTP in the presence of T4 DNA polymerase and DNA ligase of *E.coli*, then purification according to the method described above,

d) placing said transformed host cell in culture and recovering said polypeptide from said culture.

2. A method for the preparation of a polypeptide encoded by a region of the HIV or SIV genome, said method comprising:

a) amplifying the nucleic acid encoding said polypeptide with at least two primers, wherein said first primer is complementary to a region of nucleotides of the nucleic acid of said genome, said second primer is complementary to a region of nucleotides of the strand of DNA complementary to said nucleic acid of said genome, wherein said regions of nucleotides are separated by about 100 to about 1100 base pairs when said complementary strands are hybridized to form one double-stranded nucleic acid, and said primer is selected from the group consisting of:

MMy1:	TGG	CGC	CCG	AAC	AGG	GAC			
	TGG	CGC	CTG	AAC	AGG	GAC			
MMy2:	GGC	CAG	GGG	GAA	AGA	AAA	A		
	GGC	CCG	GCG	GAA	AGA	AAA	A		
	GGC	CCG	GAG	GAA	AGA	AAA	A		
MMy3:	TGC	CCA	TAC	AAA	ATG	TTT	TA		
	TGC	CCA	CAC	TAT	ATG	TTT	TA		
MMy4:	TGC	ATG	GCT	GCT	TGA	TG			
	TGC	ATA	GCT	GCC	TGG	TG			
MMy4B:	CTT	TGC	ATG	GCT	GCT	TGA	TG		
	CTC	TGC	ATA	GCT	GCT	TGC	TG		
MMy4Ba:	CAT	CAA	GCA	GCC	ATG	CAA	AG		
	CAC	CAG	GCA	GCT	ATG	CAG	AG		
MMy28:	AGG	GCT	GTT	GGA	AAT	GTG	G		
	AGG	GCT	GTT	GGA	AGT	GTG	G		
MMy28a:	CCA	CAT	TTC	CAG	CAT	CCC	T		
	CCA	CAT	TTC	CAG	CAG	CCC	T		
	CCA	CAT	TTC	CAG	CAC	CCC	T		
MMy18:	GAT	AGA	TGG	AAC	AAG	CCC	CAG		
MMy19:	TCC	ATT	TCT	TGC	TCT	CCT	CTG	T	
MMy29:	TAA	AGC	CAG	GAA	TGG	ATG	GCC	CAA	
	TAA	AGC	CAG	GAA	TGG	ATG	GAC	CAA	
MMy29a:	TTG	GGC	CAT	CCA	TTC	CTG	GCT	TTA	
	TTG	GTC	CAT	CCA	TTC	CTG	GCT	TTA	
MMy30:	TGG	ACT	GTC	AAT	GAC	ATA	CAG	AA	
	TGG	ACT	GTC	AAT	GAT	ATA	CAG	AA	
MMy30a:	TTC	TGT	ATG	TCA	TTG	ACA	GTC	CA	
	TTC	TGT	ATG	TCA	TTG	ACT	GTC	CA	
MMy31:	CAT	GGG	TAC	CAG	CAC	ACA	AAG	G	
MMy31a:	CCT	TTG	TGT	GCT	GGT	ACC	CAT	G	
MMy32:	TGG	AAA	GGT	GAA	GGG	GCA	GT		
	TGG	AAA	GGT	GAA	GGA	GCA	GT		
MMy32a:	ACT	GCC	CCT	TCA	CCT	TTC	CA		
	ACT	GCC	CCT	TCT	CCT	TTC	CA		
	ACT	GCC	CCT	TCC	CCT	TTC	CA		
MMy12:	AGA	GAC	TCT	TGC	GGG	CGC	GTG		
MMy13:	ATA	TAC	TTA	GAA	AAG	GAA	GAA	GG	
MMy13a:	CCT	TCT	TCC	TTT	TCT	AAG	TAT	AT	
MMy14:	AGC	TGA	GAC	AGC	AGG	GAC	TTT	CCA	
MMy20:	TAT	GGA	GGA	GGA	AAA	GAG	ATG	GAT	AGT
MMy21:	TAG	CAC	TTA	TTT	CCC	TTG	CTT	T	
MMy21a:	AAA	GCA	AGG	GAA	ATA	AGT	GCT	A	
MMY22:	CCC	TTG	TTC	ATC	ATG	CCA	GTA	T	
MMy23:	ATG	TCA	GAT	CCC	AGG	GAG	A		
MMy24:	CCT	GGA	GGG	GGA	GGA	GGA	GGA		
MMy5:	CCA	ATT	CCC	ATA	CAT	TAT	TGT	GCC	CC
MMy5a:	GGG	GCA	CAA	TAA	TGT	ATG	GGA	ATT	GG
MMy6:	AAT	GGC	AGT	CTA	GCA	GAA	GAA	GA	
MMy7:	ATC	CTC	A0G	AGG	GGA	CCC	AGA	AAT	T
MMy7a:	AAT	TTC	TGG	GTC	CCC	TCC	TGA	GGA	T
MMy8:	GTG	CTT	CCT	GCT	GCT	CCC	AAG	AAC	CC
MMy8a:	GGG	TTC	TTG	GGA	GCA	GCA	GGA	AGC	AC
MMy9:	ATG	GGT	GGC	AAG	TGG	TCA	AAA	AGT	AG
	ATG	GGT	GGC	AAA	TGG	TCA	AAA	AGT	AG
MMy9a:	CTA	CTT	TTT	GAC	CAC	TTG	CCA	CCC	AT
MMy78:	TAT	TAA	CAA	GAG	ATG	GTG	G		
MMy89:	CCA	GCA	AGA	AAA	GAA	TGA	A		
MMy89:	TTC	ATT	CTT	TTC	TTG	CTG	G		
MMy10:	AAA	AGA	AAA	GGG	GGG	ACT	GGA		
MMy10a:	TCC	AGT	CCC	CCC	TTT	TCT	TTT		
MMy11:	AAA	GTC	CCC	AGC	GGA	AAG	TCC	C	
MMy15:	GAT	TAT	GGA	AAA	CAG	ATG	GCA	GGT	GAT
MMy16:	GCA	GAC	CAA	CTA	ATT	CAT	CTG	TA	
MMy16a:	TAC	AGA	TGA	ATT	AGT	TGG	TCT	GC	
MMy17:	CTT	AAG	CTC	CTC	TAA	AAG	CTC	TA	